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BRIEF REPORT

SWOG S1400D (NCT02965378), a Phase II Study of the Fibroblast Growth Factor Receptor Inhibitor AZD4547 in Previously Treated Patients With Fibroblast Growth Factor Pathway–Activated Stage IV Squamous Cell Lung Cancer (Lung-MAP Substudy)

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ABSTRACT

Background: S1400D is a biomarker-driven therapeutic substudy of Lung-MAP evaluating the fibroblast growth factor (FGF) receptor (FGFR) inhibitor AZD4547 in patients with FGF pathway-activated squamous cell. This is the first phase II trial to evaluate AZD4547 as a targeted approach in patients with previously treated FGFR-altered squamous cell NSCLC and is the first demonstration of successful implementation and conduct of a national umbrella protocol in this disease setting.

Methods: Eligible patients had tumoral FGFR alteration or mutation and had progressive disease after at least one line of platinum-based systemic therapy. Patients received AZD4547 80 mg twice daily orally. Primary endpoint was response by Response Evaluation Criteria in Solid Tumors version 1.1; secondary endpoints included progression-free survival, overall survival, and duration of response (DoR).

Results: Ninety-two patients were assigned to S1400D, 43 were enrolled, and 27 AZD4547-treated patients were evaluable. Evaluable patients were predominantly white (n = 24, 89%), median age 66 years (range, 49–88 years old), and female (n = 7, 26%). FGFR alterations included FGFR1 amplification (n = 23; 85%), FGFR3 amplification (n = 2; 7%), FGFR3 S249C (n = 2; 7%), and FGFR3 fusion (n = 1; 4%). Treatment with ADZ4547 was well tolerated; grade 3 adverse events occurred in six patients, and one patient had grade 4 sepsis. Of 27 response-evaluable patients, 1 patient with FGFR3 S249C had unconfirmed partial response with a DoR of 1.5 months and 1 patient with FGFR1 amplification had a confirmed partial response with a DoR of 2.9 months (7%, 95% confidence interval [CI]: 0%–17%). Median progression-free survival and overall survival for the AZD4547-treated cohort were 2.7 months (95% CI: 1.4– 4.5 months) and 7.5 months (95% CI: 3.7–9.3 months).

Conclusions: AZD4547 had an acceptable safety profile but minimal activity in this predominantly FGFR1/FGFR3–amplified cohort. Evaluation of other targeted agents in Lung-MAP is ongoing.

Keywords: LUNG-MAP; SWOG1400; FGFR inhibitor

Introduction

Squamous cell NSCLC (SqNSCLC) comprises approximately 20% to 30% of all cases of NSCLC.[1] In contrast to the therapeutic advances seen in nonsquamous NSCLC, including molecular characterization and use of targeted therapy for relevant actionable oncogenic driver mutations (e.g., *EGFR*, *ALK* receptor tyrosine kinase [*ALK*]), there has been limited progress in the personalized medicine approaches for SqNSCLC.[2] Platinum-based combination therapy currently remains the backbone of first-line systemic palliative therapy for advanced SqNSCLC, with modest improvement in outcomes seen with the addition of agents such as the EGFR monoclonal antibody necitumumab, vascular endothelial growth factor targeting with ramucirumab, and afatinib in molecularly unselected patients. In the second-line setting, the paradigm of therapy for SqNSCLC has changed significantly with the approval of immune checkpoint inhibitors.

Molecular genotyping has led to the potential application of targeted agents for prevalent mutations in SqNSCLC. The Lung Master Protocol (Lung-MAP, SWOG S1400) is an umbrella protocol which contains a next-generation sequencing (NGS) screening component and multiple independently conducted and analyzed treatment substudies.[3] The overarching goal of the umbrella master protocol is to genomically screen a large population of previously treated SqNSCLC patients to evaluate targeted therapies (or combinations) in biomarker-driven substudies and immunotherapy combinations that can lead to approval of efficacious regimens. Here we report on results of SWOG S1400D, a phase II biomarker-driven therapeutic substudy of Lung-MAP evaluating the fibroblast growth factor receptor (FGFR) inhibitor AZD4547 in patients with *FGFR* pathway–activated SqNSCLC after failure of platinum-based therapy.[4] Amplifications of *FGFR1* have been described in up to 20% of SqNSCLC cases with mutations and fusions in *FGFR2* and *FGFR3* occurring at a lower incidence (each less than 4%).

In preclinical studies, AZD4547 is active against tumor cell lines and tumors bearing a broad range of *FGFR* amplifications/mutations, and AZD4547 induces tumor regression or stasis in patient-derived explant xenograft models carrying FGFR1 gene amplification.[4,5] In a small clinical study in SqNSCLC there was at least one partial response (PR) among the 14 patients treated with AZD4547, and that patient carried *FGFR1* amplification.[6] These preclinical and early clinical data coupled with the lack of significant long-term safety concerns for the drug administered as monotherapy led to the development of S1400D using AZD4547 as potential targeted therapy for FGFR-positive SqNSCLC.

Patients and Methods

Patients with previously treated and histologically proven SqNSCLC were eligible for the Lung-MAP protocols' previously described eligibility criteria.[3] Substudy eligibility was determined based on an NGS-based mutational analysis of the patient's tumor. Mutational

analysis, including determination of tumor mutational burden (TMB), was performed on archival formalin-fixed paraffin-embedded tumor specimens using FoundationOne (Foundation Medicine, Cambridge, Massachusetts). The full list of alterations evaluated is included in Supplementary Table 1. The FGFR alterations required for eligibility to S1400D were *FGFR1/FGFR2/FGFR3* amplifications, fusions, or substitutions. Amplification was defined as greater than or equal to six estimated copies (or greater than or equal to seven for triploid or greater than or equal to eight for tetraploid samples). In addition, eligibility to S1400D included age greater than or equal to 25 years; Zubrod performance score of 0-2; measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1; adequate hematologic, hepatic, cardiac, renal, and ophthalmologic function; and no impairment of gastrointestinal function or gastrointestinal disease that could significantly alter absorption of AZD4547. Exclusion criteria included leptomeningeal disease; symptomatic, untreated brain metastases; and chemotherapy within 21 days before registration. Written informed consent was required from all patients before enrollment in the master protocol and a separate consent form was required for treatment on the specific substudy.

AZD4547 was administered orally at 80 mg twice daily. Treatment cycles were 21 days. Fasting was not required; however, AZD4547 was not administered with foods known to modulate CYP3A4 or CYP2D6 enzyme activity. Disease assessment occurred every two cycles, and treatment could continue until progression. Dose reductions and adjustments were discussed with the study chair and were followed as specified in the protocol.

Table 1. Patient Demographics and Characteristics (n = 27)

Characteristics	n (%)
Age, median (range), years	66.3 (49-88)
Male	20 (74)
Performance Status	
0	4 (15)
1	23 (85)
2	0 (0)
Race/ethnicity	
White	24 (89)
Black	3 (11)
Asian	0 (0)
Hispanic	2 (7)
Number of prior lines of therapy for stage IV disease	
0	2 (7)
1	22 (82)
2 or more	3 (11)
Smoking status	
Current smoker	11 (41)
Former smoker	16 (59)
Never smoker	0 (0)

Statistical Considerations

The primary objective for S1400D was to evaluate the response rate (RR) (confirmed and unconfirmed, complete, and partial) in patients treated with AZD4547. The

Table 2. Gene Alterations Detected on FMI NGS Screening (n = 27)[a]

	n (%)
Study eligibility alterations (FGFR+)	
FGFR1 amplification	23 (85)
FGFR3 S249C	2 (7)
FGFR3 amplification	2 (7)
FGFR3 fusion	1 (4)
Number of FGFR gene alterations	
1	26 (96)
2	1 (4)
TMB score (n = 25)[b]	
Median	10.88
Range	2.42-21.77
Interquartile range	8.46-15.72
<10	12 (48)
≥10	13 (52)
Other concomitant gene alterations	
Short variants	
TP53	26 (96)
MLL2	5 (19)
CDKN2A, NF1, NFE2L2	3 (11)
FBXW7, LRP1B, PAX5, SMAD4	2 (7)
BRCA2, CREBBP, DAXX, EP300, GATA2, HRAS, KDM6A, MYD88, NOTCH1, PALB2, PIK3R1, PTCH1, PTEN, RB1, RNF43, STAG2, TSC1	1 (4)
Copy number alterations	
ZNF703	18 (67)
MYST3	10 (37)
SOX2	9 (33)
PIK3CA, RICTOR	6 (22)
MYC	5 (19)
CDKN2A, CDKN2B	4 (15)
AKT2, FGF10	3 (11)
CTNNB1, FGF12, GNAS, IRS2, KDM5A, KDM6A, NF1, PTEN	2 (7)
AKT1, ARFRP1, ARID1A, AURKA, AXL, BAP1, BCL2L2, CCND1, CDK8, ERBB2, ERBB3, FGF19, FGF3, FGF4, FLT3, JUN, KDR, KIT, KRAS, MCL1, MTOR, NFKBIA, NKX2-1, NRAS, PDGFRA, PRSS8, RB1, RPTOR, SRC, TSC1, ZNF217	1 (4)
Rearrangements	
LRP1B	2 (7)
ARID1A, BRCA2, CDKN2A, PRDM1, PTEN, ROS1	1 (4)

[a]Full list of alterations is included in Supplementary Table 1.
[b]TMB was calculated as the number of somatic, coding, short variants, excluding known driver mutations, per megabase of the genome interrogated; TMB score was not evaluable for two patients.
FMI, Foundation medicine; NGS, next-generation sequencing; FGFR, fibroblast growth factor receptor; TMB, tumor mutational burden.

Table 3. Adverse Events Attributed to Treatment (n = 27)

	Grade		
AE	3	4	5
Dyspnea	1 (4)		
Fatigue	1 (4)		
Hyponatremia	1 (4)		
Lung infection	1 (4)		
Lymphocyte count decreased	1 (4)		
Mucositis oral	1 (4)		
Retinopathy	1 (4)		
Sepsis		1 (4)	
Maximum grade of any AE	6 (22)	1 (4)	0

Values shown are n (%).
AE, adverse event.

sample size (n = 40) was based on a design with 91% power to rule out a RR of 15% at the one-sided 5% level if the true rate was 35%. A key secondary objective was an investigator assessment of median progression-free survival (mPFS). If the RR was less than 25% but the mPFS was at least 4.5 months, this would be considered sufficient evidence to continue to phase III. With 40 patients, this design had 90% power to rule out an mPFS of 3 months or less if the true mPFS was 6 months at the 5% one-sided level. Binary proportions and associated 95% confidence intervals (CIs) were estimated. Survival distributions were estimated using the Kaplan-Meier method and the Brookmeyer-Crowley method was used to estimate CIs.

Results

Baseline patient characteristics for the 27 evaluable patients are displayed in Table 1. Frequency of FGFR alterations among evaluable patients were as follows: *FGFR1* amplification (n = 23, 85%); *FGFR3* amplification (n = 2, 7%); *FGFR3* S249C (n = 2, 7%); and *FGFR3* fusion (n = 1, 4%) (Table 2). All but one patient had one *FGFR* alteration detected; one patient had two *FGFR*

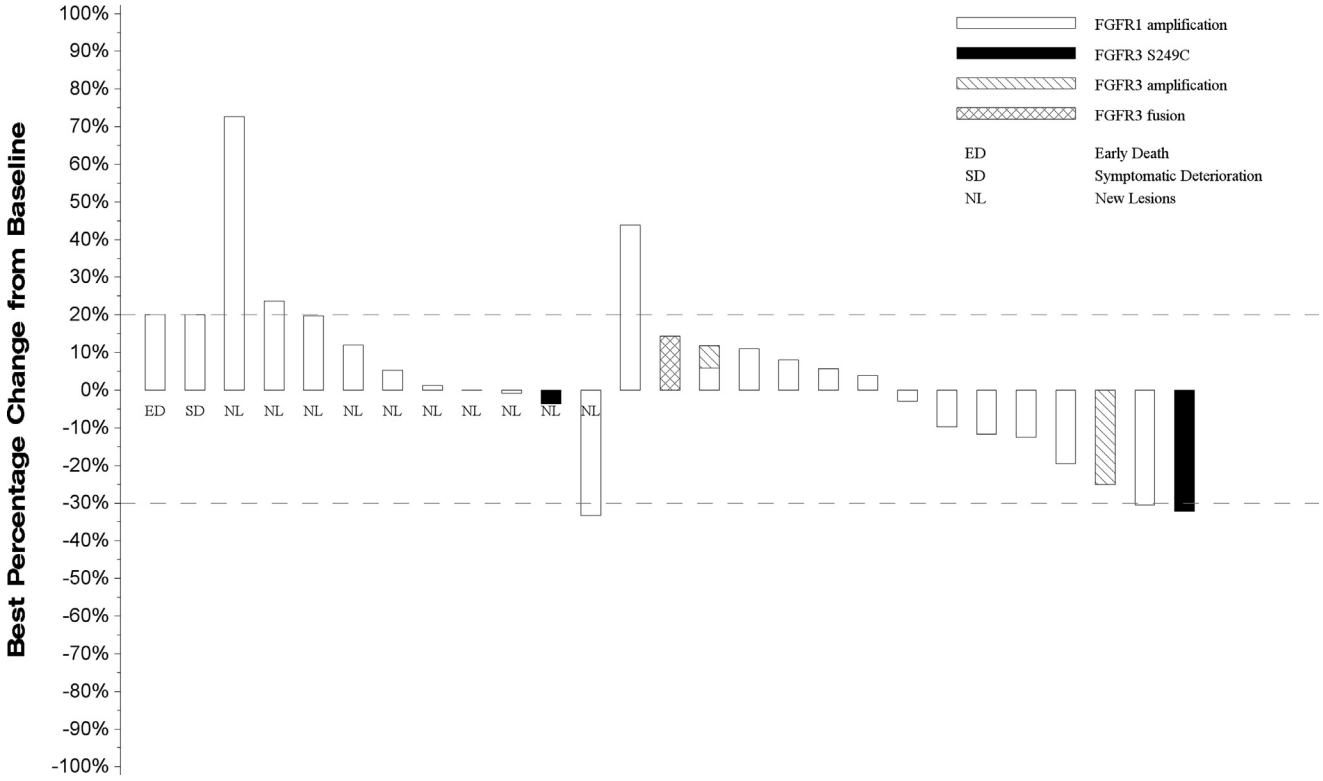

Figure 1. Waterfall plot of response to AZD4547. Each vertical bar represents a patient's best percent change in tumor burden when compared to baseline as defined by RECIST 1.1. Only patients with measurable disease at baseline are presented in the plot. Patients who did not have follow up tumor disease assessment were presented at the very left of the plot marked with IA. Patients who had new lesions appear at their first follow-up assessment were presented with percentage change in target lesions and marked with NL. Patients who had unequivocal progression in non-target lesions at their first follow-up assessment were presented with percentage change in target lesions and marked with UP. Patients who expired prior to the first scheduled disease assessment and the death can reasonably be assumed to be due to disease progression were represented graphically as a 100% increase in tumor burden. Patients who had symptomatic deterioration at first disease assessment were marked as SD. Patients who expired prior to disease assessment, but the death was not due to disease were marked as ED. Negative numbers represent decrease in tumor burden from baseline while positive numbers represent increase in tumor burden from baseline. cFGFR, fibroblast growth factor receptor.

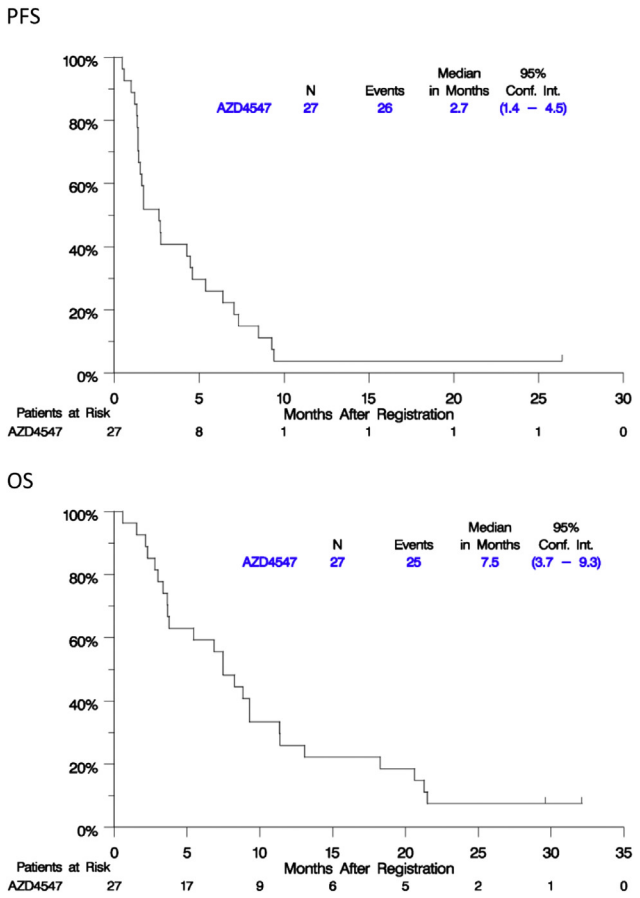

Figure 2. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS). (*A*) PFS. (*B*) OS. Conf. int., confidence interval.

alterations. The median and range TMB scores were 10.88 (range: 2.42–21.77), with 13 (52%) patients having TMB scores greater than or equal to 10.

Overall, treatment with AZD4547 was well tolerated (Table 3). Treatment-related grade 3 adverse events (AEs) were seen in six patients. One patient had grade 4 sepsis possibly related to study drug. There were no grade 5 AEs. Patients received a median of two cycles (range: 1–12, interquartile range: 2–3) of AZD4547.

Of 27 response-evaluable patients, 2 patients had PR (7%, 95% CI: 0%–17%): 1 with *FGFR3* S249C gene mutation and 1 with *FGFR1* amplification, with a duration of response of 1.5 months and 2.9 months, respectively. The magnitude of response for the 27 evaluable patients by submutation is depicted in the waterfall plot in Figure 1. mPFS was 2.7 months (95% CI: 1.4–4.5 months). Median overall survival (OS) was 7.5 months (95% CI: 3.7–9.3 months) (Fig. 2). The 1- and 2-year OS estimates were 25.9% and 7.4%, respectively. Forest plot analyses for PFS and OS showed a significantly worse OS (but not PFS) for current versus former smokers (there were no never-smokers in this study) (Supplementary Fig. 1). Current smokers had a four-fold increased risk of death over former smokers (hazard ratio = 4.12; 95% CI: 1.53–11.10; $p = 0.005$). However, no subgroup derived significant benefit from treatment with AZD4547.

Discussion

Unfortunately, despite early promise, AZD4547 showed minimal antitumor activity in this previously treated, genomically selected SqNSCLC patient population with *FGFR* pathway activation. In this cohort, *FGFR1* amplification was the most common alteration followed by *FGFR3* amplification. Two patients had short-lived PRs, one of which was seen in a patient with *FGFR3* S249 C gene mutation, and the other one in a patient with *FGFR1* amplification, consistent with previous reports of activity of this drug in an amplified tumor. Very few patients had *FGFR* mutations or fusions; therefore, conclusions regarding efficacy in this subpopulation should await further investigation. AZD4547 was overall well tolerated, and no significant safety signals were noted.

We believe there are several reasons why this trial was not successful. First, the biology of SqNSCLC remains complex. Unlike oncogene-addicted adenocarcinomas, such as *EGFR* mutant, or *ALK* rearranged NSCLC, squamous cell lung cancers often have multiple mutations without a single driver mutation. They are characterized by a high overall mutational burden, at a rate of 8.1 mutations per megabase. Almost all patients display somatic mutations of tumor protein p53 (*TP53*), and the most commonly observed alterations are in pathways associated with tumor growth, proliferation, and survival. Because the growth and signaling pathways are complex, we hypothesize that one drug may not be adequate to effectively inhibit the growth of the *FGFR*-altered tumors studied in this trial. Additionally, *FGFR* amplifications are biologically different from *FGFR* fusions or mutations in that they represent a potentially heterogeneous aberration, with different response to targeted therapies and potentially different resistance mechanisms. It is entirely possible that as we target the initial *FGFR* amplification there may be complex resistance pathways in place to enable tumor growth and survival. It is also possible that AZD4547 was just not effective; however, selection of the drug was based on preclinical activity and evidence of clinical activity in a phase I study.

Although this was a negative study, there are several positive takeaways. The Lung-MAP study was broadly designed to include patients with previously treated squamous cell carcinoma. The protocol was swiftly amended to alter randomization when standard-of-care was changed, and multiple substudies such as S1400D were designed that could open and close autonomously and allow for rapid identification and evaluation of targeted agents. Each substudy was then redesigned as a phase II study, and futility analyses were built in to enable early termination as in this study. Importantly, S1400D

represents a successful and extensive collaboration between industry, academia, and national organizations such as the Foundation for the National Institutes of Health and the National Cancer Institute, and evaluation of other targeted agents in Lung-MAP is ongoing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.05.041.

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